

SOCIAL DEMOGRAPHIC CHANGE AND AUTISM*

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Parental age at child's birth—which has increased for U.S. children in the 1992–2000 birth cohorts—is strongly associated with an increased risk of autism. By turning a social demographic lens on the historical patterning of concordance among twin pairs, we identify a central mechanism for this association: de novo mutations, which are deletions, insertions, and duplications of DNA in the germ cells that are not present in the parents' DNA. Along the way, we show that a demographic eye on the rising prevalence of autism leads to three major discoveries. First, the estimated heritability of autism has been dramatically overstated. Second, heritability estimates can change over remarkably short periods of time because of increases in germ cell mutations. Third, social demographic change can yield genetic changes that, at the population level, combine to contribute to the increased prevalence of autism.

This article considers and provides a solution to an intriguing puzzle that involves squaring the following four contradictory observations. First, the scientific community widely regards autism to be the most genetic of all neuropsychiatric disorders (Lamb et al. 2000). Second, autism prevalence has increased rapidly (roughly tenfold) over the past four decades (Cohen et al. 2005). Third, fundamental changes in the human gene pool are highly unlikely in one or two generations and have never been observed previously. Thus, if autism is related to genes, it seems axiomatic that the genetic foundation for the increased prevalence of autism rests on a gene-environment interaction involving a change in the environment. Fourth, molecular genetic research has identified the genetic basis for less than 15% of autism cases, and no single known genetic cause explains more than 1%–2% (Abrahams and Geschwind 2008; Wang et al. 2009). A typical response to such a riddle might be to wait for the molecular genetic research to catch up and identify a genetic cause of autism. The evidence presented in this article suggests instead that we can start to square this circle of conundrums by focusing our attention toward a new, and profoundly different, observation: the observation of genetic influence on autism through de novo mutations arising from social demographic change. Here, the change of interest is increased parental age.

There is a strong relationship between parental age and autism. The one study (King et al. 2009) that decomposes maternal and paternal age—and confounding cohort effects—identifies maternal age as riskier than paternal age (using the California data deployed in this analysis). Specifically, the categorical risks associated with maternal age over 40 years ranged from 1.27 (95% confidence interval [CI] = 0.95, 1.69) to 1.84 (95% CI = 1.37, 2.47), and the risk associated with advanced paternal age ranged 1.29 (95% CI = 1.03, 1.6) to 1.71 (95% CI = 1.41, 2.08) over the study period reported here. Over the same time, the proportion of children born whose parents were age 35 or older at birth increased rapidly: from 24.3% in 1992 to 36.2% in 2000. We propose that the relationship between advanced

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parental age and increased autism risk arises at least in part from *de novo* mutations, a possibility we assess through a twin design.¹

To anticipate the main results of this article, we first demonstrate that *autism heritability*—defined in the narrow sense as the difference in concordance for autism between monozygotic (MZ) and dizygotic (DZ) twins—is not as significant as typically believed. This finding points to the need to consider prenatal, social, and environmental influences on autism risk. One social factor—parental age at child's birth, which has increased substantially for children born during the 1992–2000 birth cohorts—is strongly associated with an increased risk of autism. We identify a central mechanism for this association: *de novo* mutations, which are deletions, insertions, and duplications of DNA in the germ cells (sperm or egg) that are not present in the parents' DNA. Affecting the offspring's DNA sequence, *de novo* mutations may lead to genetic predisposition to autism, yet they do not require fundamental changes in the human gene pool.² We analyze the temporal pattern of concordance for autism in twin pairs over time and show that this pattern reveals increasing genetic effects on autism. Finally, we design and report findings of a critical test that provides exceptionally detailed support for the idea that *de novo* mutations are associated with autism. Along the way, we show that a sociological eye on the rising prevalence of autism gives rise to three major discoveries. First, the estimated heritability of autism—from family studies, where heritability refers to MZ-DZ difference in concordance—has been dramatically overstated. Second, heritability estimates can change over short periods of time because of the rising frequency of germ cell mutations, and there is evidence that the heritability of autism is increasing. Third, social demographic change in parents can yield genetic changes that, at the population level, combine to contribute to the increased prevalence of autism. In the discussion, we consider how a demographic lens, sensitive to temporality, can shed new light on autism and perhaps therefore influence the direction of subsequent research.

BACKGROUND

Autism is a developmental disorder that profoundly limits the ability of those with the disease to communicate, form and maintain social relations, and respond to environmental stimuli. The incidence of autism in the United States (and elsewhere) has increased rapidly over the past two to three decades. In California, where our data were collected and where the most systematic records have been kept, the number of autism cases increased 634% between 1987 and 2002 (California Department of Developmental Services 2003). This is a striking increase. Equally striking is the absence of consensus with respect to causes for increased prevalence. In fact, with the exception of being male and parental age—factors long recognized to be associated with increased risk—newer studies routinely report findings in tension with previous research.

Hundreds of studies have investigated hundreds of factors believed to be associated with both the incidence and increased prevalence of autism. In addition to genetic predisposition, scholars have argued that prenatal conditions, obstetric complications, parental characteristics, environmental toxicants, and the availability of school and community resources could all potentially be associated with the number of autism cases (Grandjean and Landrigan 2006; Kolevzon, Gross, and Reichenberg 2007; Palmer et al. 2005; Reichenberg et al. 2006). Covariates identified in previous work are extensive, ranging from premature

1. Our twin design limits our inferences to twin births. Although it is likely that the increased risk for autism is associated with *de novo* mutations, we cannot rule out an unobserved factor, such as fertility treatments.

2. As one of our anonymous reviewers helpfully pointed out, *de novo* mutations are genetic and may be heritable (in the sense that they may be passed on to children of the next generation), but they are unlikely to be identified with genomic association studies insofar as they are independently arising mutations that are likely to involve a wide variety of loci on the genome.

birth, breech birth, and low APGAR score at five minutes to parental characteristics, such as socioeconomic status, education, age, race, occupation, and history of schizophrenia (Croen, Grether, and Selvin 2002; Larsson et al. 2005). At the community level, resources available for screening, increased service availability, the density of pediatricians in a community, environmental toxicity, the number of students per school, and percentage of students receiving a free lunch have been tied to rates of autism (Lathe 2006; Palmer et al. 2005). Most of these associations are not causally related to increased prevalence. Instead, a disproportionate body of research seemingly confuses correlated time series with cause, producing an efflorescence of factors associated with autism: a veritable laundry list of variables to consider. One reason for this state of epidemiological confusion is that autism, by virtue of increased prevalence, is a moving target. The composition of those with autism changes over time; hence, our understanding of risk factors is also temporally sensitive, dependent on the observation window and spatial context in which the study is based (King et al. 2009). In this article, we show how a more nuanced understanding of temporal dynamics leads to new insights.

In broad sweep, three ideas motivate most of the current accounts of the increased prevalence of autism. The first account is that increased prevalence stems from diagnostic dynamics, driven by process of diagnostic change, substitution, and drift (Shattuck 2006). Support for this hypothesis arises from the fact that early on in the epidemic, one could not observe the classic socioeconomic status–health gradient and that autism spectrum disorders (ASD) appeared to be a diagnosis of choice for middle- and upper-class parents whose children would be otherwise diagnosed as mildly or severely retarded, a disorder still associated with increased stigma. King and Bearman (2009) estimated that roughly 25% of the increased prevalence of autism is associated with diagnostic change on the mental retardation (MR) pathway. Using a different estimation strategy, Bishop et al. (2008) suggested that one-third of the caseload arises from diagnostic dynamics. Consistent with this idea is the corresponding claim that the real incidence of autism in the population was previously underreported to avoid the stigma associated with autism when it was perceived to be a psychogenic rather than a developmental disorder (Liu, King, and Bearman forthcoming).

The second account centers on environmental toxicants, in interaction with genetic factors, none of which are well understood. Most of the evidence for such a link is indirect. Base metals that are clearly implicated in developmental disorders are most commonly suspected; as of this writing, 272 candidate toxicants have been identified as potentially linked to autism (Grandjean and Landrigan 2006). The environmental impact hypothesis remains robust principally because the increase in autism caseloads is consistent with observed increase in environmental degradation. Finally, there is clear evidence that autism has a significant family and genetic component net of gene-environment interactions, although molecular genetic research has identified a genetic basis for less than 15% of all autism cases, and no single known genetic cause accounts for more than 1%–2% of all cases (Abrahams and Geschwind 2008; Wang et al. 2009). The key support that autism is a genetic disorder arises from the reported difference in concordance rates for autism in identical and fraternal twin pairs, and a high recurrence risk in siblings.

There is no reason to believe that any one of these frameworks is wrong, and there are many reasons to believe that the increased prevalence of autism is the outcome of multiple self-reinforcing processes that invoke all three of these core explanations. We can, however, make progress by recognizing that the increase in reported autism prevalence—at least that component not stemming from increased surveillance and ascertainment—must be tied to a social change process that invokes a biological mechanism associated with neurodevelopmental processes. This is the strategy undertaken in this article, wherein we consider twin, full-sibling, and half-sibling concordance for autism over time in order to understand how social and genetic factors intersect to induce the rising prevalence of autism.

The Evidence for High Heritability of Autism

To date, the strongest evidence supporting the idea that autism is a genetic disorder arises from twin and family studies. Previous twin studies on full syndrome autism have reported high pairwise concordance rates in identical (MZ) twins (36%–96%) and low concordance rates in fraternal (DZ) twin pairs (0%–31%) (Bailey et al. 1995; Folstein and Rutter 1977; Ritvo et al. 1985; Steffenburg et al. 1989). Because MZ twins share 100% of their genes while DZ twins share only around 50%, a large difference between MZ and DZ concordance rates is regarded as strong evidence for genetic influences. The recurrence risk of autism in siblings is reported to range from 3%–9%, which is much higher than the population rate of 10 in 10,000 children (Baird and August 1985; Bolton et al. 1994; Piven et al. 1990; Ritvo et al. 1989).³ Relatives of a child with autism are also more likely to have broadly defined autism spectrum traits than controls (Szatmari et al. 2000).

One significant problem with these reports is that they are based on small convenience samples and/or referrals. Where recruitment of pairs into studies relies on such samples, heritability estimates are biased upward because pairs that are more similar on unobserved characteristics are more likely to be enrolled. In this case, the conclusion that the concordance of full-spectrum autism is much higher in MZ than DZ twins has come from studies with a total combined population of 110 pairs. This is not a robust platform from which to make inference. Moreover, the epidemiological patterns of autism do not conform to simple Mendelian expectations: most autism cases are sporadic (i.e., with no history in the family), and the pattern of observed concordance rates in identical twins, fraternal twins, full siblings, and relatives are inconsistent with dominant, recessive, or X-linked transmission models (Skuse 2000). This suggests that the genetic influence on autism is likely to be complex.

One important idea that we explore in detail is that Mendelian inheritance is not likely to be the core mechanisms for genetic influence. Interactions between multiple loci are much more likely to be the underlying mechanisms (Abrahams and Geschwind 2008), and recent studies suggest that the process is likely to be driven by genetic changes arising in part from *de novo* mutations of germ cells. Recent studies conducted by Sebat et al. (2007), Jacquemont et al. (2006), and others (deChristian et al. 2008; Kumar et al. 2008; Marshall et al. 2008; Morrow et al. 2008; Szatmari et al. 2007; Weiss et al. 2008) suggest that *de novo* mutations occurring in a wide range of genomic locations contribute to autism, adding support to the evidence that autism has heterogeneous genetic causes. Consequently, simple (and static) models of genetic inheritance appear inadequate to account for autism.

From a social demographic perspective, this makes sense. The autism research community has long understood that parental age is a significant risk factor for autism, but the age of parents is not something that “gets under the skin” by itself. Net of the impact of parental age (and socioeconomic status) on the probability of diagnosis and thus ascertainment, it follows that if broad social changes associated with increased age of parents plays a role in the autism epidemic, a dynamic multiple-locus model is more likely to identify the operative mechanism than the traditional Mendelian framework. This is the possibility explored in this article, wherein we consider concordance of twin pairs over time and reveal how rising parental age, which leads to greater probability of *de novo* mutations, accounts for the changes in concordance that we observe over time. To design a critical test of their role in the etiology of autism, we exploit the fact that *de novo* mutations are rare events.

3. Other studies have used a population-based sample to look at the concordance for more broadly defined autistic spectrum disorders or autistic traits (e.g., Hoekstra et al. 2007; Taniai et al. 2008). To our knowledge, no population-based study has been conducted on full syndrome autism.

Concordance in Twins and Recurrence Risk in Siblings

Measures of genetic influence based on fragile empirical foundations are suspect. To generate robust estimates of genetic influences, we need to measure concordance rates (casewise and pairwise) for autism in twins as well as recurrence risk in siblings in a representative sample. These are our central outcome measures. *Casewise concordance* (Pcw) measures the probability that a co-twin will be affected (with a given disorder), given that the other twin is affected. *Pairwise concordance* (Ppw) measures the proportion of concordant (both twins are affected) pairs in all pairs with at least one twin who is affected.

Twins may be concordant or discordant on some characteristic of interest: in this case, autism. Let n_c be the number of concordant pairs and n_d be the number of discordant pairs. It follows that in same sex (SS) twins, the casewise concordance rate is equal to $[2n_c / (2n_c + n_d)]$ because we can assume interchangeability of twins. This means we can assume that the risk of twin A being affected given that twin B is affected is the same as the risk of twin B being affected given that twin A is affected. For many disorders, interchangeability of twins can be assumed for opposite sex (OS) twins as well, but for autism, interchangeability cannot be assumed because boys are four times more likely than girls to be affected. Thus, separate casewise concordance rates need to be estimated to measure (1) the likelihood that a male co-twin would also have autism given that his female twin sibling was affected $[2n_c / (2n_c + \text{all pairs with an affected female})]$; and (2) the likelihood that a female co-twin would also have autism given that her male twin sibling was affected $[2n_c / (2n_c + \text{all pairs with an affected male})]$. In (1), the female twin with autism is referred to as the *proband*; in (2), the male twin with autism is referred to as the *proband*, by convention.

An advantage of casewise concordance rates in twins is that they are directly comparable with recurrence risk estimated in other relatives. *Recurrence risk* is a measure of the likelihood that a condition recurs in the family by affecting another sibling. We determine recurrence risk among sibling pairs by the later sibling method (Ritvo et al. 1989), which is the proportion of younger siblings born after an older child with autism (again, referred to as the proband) who also have autism. *Stoppage*—parents stopping to have more children after having an affected child—is less of an issue with this method because the recurrence risk is evaluated only among families with children born after a child with autism. We further differentiated recurrence risk in full and half-siblings. To examine the effect of gender and potential differential genetic liability, we calculated casewise concordance rates and recurrence risk by the sex pairing of the proband and the co-twin/sibling. Casewise concordance rates are reported with 95% confidence intervals estimated based on asymptotic (maximum likelihood estimation) variance. Recurrence risk is reported with Wilson 95% confidence intervals (Agresti and Coull 1998).

In short, we are interested in the extent to which autism runs in families. As with all other traits and behaviors that may run in families, one efficient way to consider if they do is to calculate twin concordance and sibling recurrence risk. For this, it is critical to work with large representative samples that do not arise from self-selection or self-nominated membership in twin registries, or from convenience samples of twins, all of which are biased toward selection of similar pairs, and hence amplify the extent to which pairs are concordant on some trait.

DATA AND METHODS

Our data come from California, where the 21 regional centers of the statewide Department of Developmental Services (DDS) provide services to the vast majority (estimated to be more than 85%) of people with autism.⁴ This study was based on the DDS client data for

4. See Croen, Grether, and Selvin (2002). The estimation was based on a comparison between the DDS data

the approximately 20,000 persons born between 1992 and 2000 who were diagnosed with autism. The DDS provides service to patients with autistic disorder. Individuals diagnosed with other developmental disorders, including Asperger's disorder, childhood disintegrative disorder, Rett's disorder, and pervasive developmental disorder—not otherwise specified (PDD-NOS) are ineligible for services provided through the DDS. Thus, our study focuses on “full-syndrome” autism—for which diagnostic dynamics associated with increased prevalence are less intense—and not spectrum disorders, which are likely subject to more diagnostic movement.

Identifying Twins and Siblings

To identify the co-twins and siblings of all individuals with autism, we first linked the DDS data of all individuals with autism to the birth master files on the 4,906,926 children born between 1992 and 2000 in California. Over time, the mean age of diagnosis has fallen precipitously, from roughly 6 to 3. Even so, we chose 2000 as the latest cohort to minimize ascertainment biases owing to missing older children: we estimated at least 95% of the 2000 birth cohort with autism would have been diagnosed by June 2006. Of the 19,436 DDS patients born between 1992 and 2000 who ever had an autism diagnosis, 16,352 (84%) were successfully linked to the birth records data. Record linkage was performed by matching probabilistically using information on patients' names, gender, date of birth, and race. Potential mismatches were manually verified. The vast majority of individuals not matched were born outside of California.

Exact matching of twin pairs on date of birth, hospital code, mother's names, mother's date of birth, and mother's country of birth yielded 39,035 SS and 17,596 OS twin pairs, of which 503 pairs had at least one child with full-syndrome autism. Exact matching on mother's names, mother's date of birth, and mother's country of birth yielded 9,496 sibling groups with at least one child with autism. Sibling groups with older siblings born before 1992 (3,871) were excluded from the analysis (because we have no information on the diagnostic status of these older siblings), yielding 5,625 eligible siblings groups with at least one child with autism. The excluded group has a slightly lower prevalence of autism than our study population because firstborn children have a higher risk for autism, but with respect to all other characteristics, they are comparable to those included. Father's surname and date of birth were used to differentiate full siblings and maternal half-siblings. For our calculation of parental age, we averaged the ages of both parents when data on both ages were available. When the father's age was missing, we used the mother's age. In short, the data on which this study is based is large and representative. Consequently, the inferences we are able to make are likely more robust than those drawn from prior work.

RESULTS

Twin Concordance and Sibling Recurrence Risk Implicates Social/Environmental Factors

Table 1 reports twin concordance and sibling recurrence risk in autism. SS twins had the highest casewise concordance rates (48.8% for males and 42.4% for females). There was no significant difference between the casewise concordance in SS males and SS female twins ($p = .398$).

The concordance in OS twins is necessarily *lower* than in SS-DZ twins because of their gender composition: one-half of the OS pairs twins must be girls (who have one-fourth of the risk of autism that boys have). In contrast, SS-DZ twin samples with at least one twin affected consist mostly of males because of the higher prevalence of autism in boys. Just

and California's special education database. The case definition of autism in the special education is unclear and is likely to include many children that do not meet the full syndrome criteria. Thus, 85% is a conservative estimate.

Table 1. Twin Concordance and Sibling Recurrence Rates

| Twin Type | Casewise Concordance (%, 95% CI) | Pairwise Concordance (%) | <i>n</i> Concordant Pairs | <i>n</i> All Pairs |
|--|--|--------------------------------|---------------------------------|----------------------------------|
| A. Twin Concordance | | | | |
| Same sex (SS) | 47.5 (41.6–53.4) | 31.1 | 98 | 315 |
| Two boys (SSM) | 48.8 (42.1–55.5) | 32.3 | 80 | 248 |
| Two girls (SSF) | 42.4 (29.2–55.6) | 26.9 | 18 | 67 |
| Opposite sex (OS) | 18.4 (11.3–25.5) | 10.1 | 19 | 188 |
| Male co-twins of a female proband | 38.8 (25.2–52.4) | — | 19 | 49 |
| Female co-twins of a male proband | 12.1 (7.0–17.2) | — | 19 | 158 |
| B. Estimated MZ and DZ Concordance Rates | | | | |
| Monozygotic males (MZM) | 57.0 (40.5–73.5) | 39.9 | — | |
| Monozygotic females (MZF) | 67.2 (42.8–91.6) | 50.6 | — | |
| Same sex dizygotic (SSDZ) | 32.9 (10.5–48.7) | 19.7 | — | |
| Sibling Type | Recurrence Risk (%, 95% CI) | | <i>n</i> With Autism | Total <i>n</i> of Siblings |
| C. Recurrence Risk in Full and Half-siblings | | | | |
| All full siblings | 9.7 (8.7–10.9) | | 272 | 2,796 |
| SS full siblings | 12.2 (10.5–13.9) | | 173 | 1,427 |
| SS male full siblings | 13.8 (12.0–15.9) | | 165 | 1,196 |
| SS female full siblings | 3.5 (1.8–6.7) | | 8 | 231 |
| OS siblings | 7.2 (6.0–8.7) | | 99 | 1,369 |
| Male full siblings of a female proband | 18.4 (13.8–24.0) | | 40 | 218 |
| Female full siblings of a male proband | 5.1 (4.0–6.6) | | 59 | 1,151 |
| Half-siblings | 3.4 (1.6–6.9) | | 7 | 208 |

the effect of gender alone would lead to a higher concordance rate in SS-DZ than in OS pairs. Against this background, it is striking that the pairwise concordance in OS twins (10.1%) observed in this study is higher than the often-cited 0% concordance in the SS-DZ twin samples (Bailey et al. 1995). The casewise concordance rate for OS twins is 18.4%, fully 2.6 times higher than the recurrence risk in OS full siblings (7.2%). Because OS twins and OS full siblings have the same genetic relatedness, the difference in recurrence risk indicates that in addition to genetic factors and also perinatal and prenatal care, social and other environmental factors must contribute to autism.

The administrative data we work with do not have a direct measure of zygosity, so we do not know from these data whether twins are MZ or DZ, which is central to the estimation of genetic influence. A simple and well-established rule that has been shown to give robust zygosity estimates has been developed for this purpose and has been widely used in research on twinning rates and a range of other research questions (Scarr-Salapatek 1971; Tong, Caddy, and Short 1997; Westergaard et al. 1997). The rule exploits the known fact that all OS twin pairs are DZ twins. Because DZ twins have an equal probability of being male and female—just as all births have such an equal probability—it follows that the number of DZ twins in SS pairs in the population equals the total number of OS twin pairs. Minor

deviations from the equal sex ratio have a negligible impact on the resulting estimates (Fellman and Eriksson 2006). As mentioned earlier, 39,035 SS twin pairs and 17,596 OS pairs were born between 1992 and 2000 in California. Let r be the proportion of MZ twins in the SS group. Using this general rule, it follows that $r = [(39,035 - 17,596) / 39,035] = 0.55$.⁵ This gives a MZ twinning rate of 4.4 in 1,000 pregnancies (21,469 of a total of 4,847,467 pregnancies). Unlike DZ twinning rates, MZ twinning rates are stable across countries and over time (Bortolus et al. 1999). Our estimated MZ twinning rate corresponds closely to the figure based on a large-scale study with direct zygosity measures—4.5 per 1,000 maternities (Derom et al. 1987).

Having estimated the value of r and given the fact that the SS concordance rate is a weighted average of the concordance rates in MZ twins and SS fraternal twins, we can estimate the MZ concordance rates by simple linear transformation. We know that the risk of autism depends on the child's sex but not on the sex of the proband.⁶ Given this, the case-wise concordance rate for MZ male pairs and MZ female pairs are estimated to be 57.0% and 67.2%, respectively. The corresponding pairwise concordance rates are 39.9% and 50.6%, respectively. These concordance rates are substantially lower than the commonly cited range of 80%–100%. On the other hand, our estimate of the casewise concordance in DZ twins is 32.9%, substantially higher than the previously reported figure of 0%.

Our estimations of MZ and DZ concordance rely on two assumptions. The first is that the sex ratio is equal at birth. The second is that the risk of autism depends on the sex of the child, not on the sex of his or her twin sibling. Minor to moderate deviations from these assumptions would not lead to different estimates. For example, if we over- or underestimated the proportion of MZ twins in the SS twin group (r) by 5%, the resulting change in our estimate of casewise concordance would have been less than 1% for MZ male twin pairs—the gender in which most cases of autism occur—and less than 6% in MZ female twin pairs. We observe similar robustness in estimates when the assumption about proband's sex and genetic liability was violated. Even if sisters posed a 30% higher risk to their co-twin than did brothers, the estimated pairwise concordance rates for MZ male pairs and MZ female pairs would be as low as 47.4% and 53.3%, respectively. Given our data, to yield a MZ pairwise concordance rate of 80% or higher (reported in prior, smaller studies, such as Steffenburg et al. [1980] and Bailey et al. [1995]), the male co-twin of a female proband would have to be exposed to at least *150 times* higher risk than the male co-twin with a male proband. This is improbable; all biological mechanisms would point to enhanced risk, if any, flowing in the opposite direction, as shown in Table 2.

A heritability estimate is a population measure of the proportion of the overall phenotypic variance attributable to genotypic variance, and it is specific to the time and

5. We estimated r based on all twin pairs born in California during the study period, not our sample of twin pairs with at least one with autism. Applying the Weinberg method to this study's sample of twin pairs is erroneous because boys are four to five times more likely to have autism than girls. Hence, DZ-SS female pairs have a lower probability to be in our sample than OS pairs merely because both girls have a lower probability of autism than the male twin in an OS pair, who thus can qualify the OS pair's inclusion in the sample. It is then imperative that the number of DZ-SS pairs would *not* equal the number of OS pairs in a sample of twin pairs with at least one twin having autism. Yet, *within* the male-male (or female-female) pairs in our sample, the proportion of MZ pairs equals to the r estimated from the population data, as should be the case in all random samples of SS pairs. Only when zygosity has a direct impact on the risk of autism (e.g., the biological process of zygotic splitting increases the risk of autism) will r estimated from the population data be a biased estimate. Note that r in our sample is independent of concordance rates. Even though the concordance rate of autism is higher in MZ twins than in DZ twins, a DZ *pair* is as likely to be included as a MZ *pair* because having *one* twin with autism is the sufficient condition for inclusion.

6. The recurrence risk for the male siblings of diagnosed female and male probands in our sample is 18.4% and 13.8%, respectively. Among female siblings, the recurrence risk is 3.5% when the proband is female and 5.1% when the proband is male. For both male and female siblings, there is no statistically significant difference by the sex of the proband ($p > .05$). These results confirm previous reports that sibling recurrence risk does not differ by the sex of the proband (Goin-Kochel, Abbacchi, and Constantino 2007; Pickles et al. 2000; Szatmari et al. 2000).

Table 2. Hypothetical Deviations From Assumptions and Their Impact on Estimated Concordances

| | Monozygotic Male Twin Pairs | | Monozygotic Female Twin Pairs | | SS Dizygotic Twin Pairs | |
|--|--------------------------------|-----------------|----------------------------------|-----------------|----------------------------|-----------------|
| | Casewise (%) | Pairwise (%) | Casewise (%) | Pairwise (%) | Casewise (%) | Pairwise (%) |
| Current Estimates | 57.0 | 39.9 | 67.2 | 50.7 | 32.9 | 19.7 |
| Deviation From the Estimated Proportion of MZ Pairs in SS Pairs | | | | | | |
| + 5% | 56.1 | 39.0 | 61.4 | 44.3 | — | — |
| –5% | 57.9 | 40.7 | 67.7 | 51.2 | — | — |
| Additional Risk Posed by Female Probands Versus Male Probands | | | | | | |
| +10% | 59.9 | 42.7 | 68.1 | 51.7 | 30.1 | 17.7 |
| +20% | 62.3 | 45.2 | 68.9 | 52.5 | 27.8 | 16.2 |
| +30% | 64.3 | 47.4 | 69.5 | 53.3 | 25.9 | 14.9 |

the population (although this is not widely recognized). Bailey et al. (1995) estimated that heritability of autism is greater than 90% under the standard ACE model, which partitions the variance into additive (allelic) genetics, shared environment, and nonshared environment components. For comparison, we estimated heritability by applying the ACE model to our data, using the expected distributions of MZ and DZ twin pairs by their joint diagnostic status. In males, the heritability of autism is estimated to be 19%. Among females, it is 63%. If the genetic liability posed by female probands were 30% higher than male probands, the heritability of autism in males would be less than 35%; for females, heritability would remain greater than 50%. Thus, an outer-bound estimate of heritability is 19%–35% for males and 50%–63% for females.

Heritability estimates can provide useful information for social scientists. Our estimates are the proportions of variance attributable to genetics within each gender. Higher heritability in females does not necessarily mean that affected females have a higher genetic liability than males; it can also occur if environmental factors are less important for girls than for boys. Differences in developmental and social environments can elicit distinct genetic expressions and, therefore, marked difference in heritability. It is also possible that different sets of genes (and their interactions) are needed to elicit autism in males and females.⁷

Independent of the differences between males and females—which are likely of sociological interest—it is clear that the heritability of autism has been wildly overestimated in previous work. Autism is very heritable but not more than other neurodevelopmental disorders. This is significant because the discovery that autism is not overwhelmingly heritable means that prenatal, social, and environmental factors likely play a substantial role in the expansion of the caseload. We now consider how one social demographic factor—a

7. Because female MZ twins are not phenotypically identical due to X-inactivation—a process by which one of the two X chromosomes in the first 70–100 cells in female fetus development is randomly inactivated (Lyon 1961)—the similarity of concordance rates for MZ males and females could suggest that the key genes for autism are unlikely to be on the X chromosome. However, if the locus of interest is not subject to random X-inactivation (Puck and Willard 1998), the theory that an imprinted X-link locus of paternal origin (i.e., a gene is expressed only when inherited from the father) is protective against autism (Skuse 2000) is consistent with a high concordance in MZ female twins, a lower concordance in DZ female twins than DZ male twins, and a lack of significant difference to the risk in the siblings of female and male probands.

relatively subtle change in age of parents at birth—is associated with autism through *de novo* mutations.

Age of Parents at Child's Birth and Relative Risk for Autism

De novo mutations are positively associated with parental age. Thus, if parental age at child's birth changes over time, we have a reason to consider whether *de novo* mutations can account for some of the increased prevalence of autism that we observe over time. As noted earlier, advanced maternal age and paternal age are significant risk factors for autism in almost all birth cohorts from 1992 to 2000 (King et al. 2009), and maternal and paternal age at child's birth increased over the period from 1992 to 2000. Mean maternal age was 26.9 (± 6.03) in 1992 and increased to 27.7 (± 6.33) by 2000. Similarly, paternal age increased from 29.6 (± 6.84) to 30.6 (± 7.11) over the same period. The increasing standard deviation, particularly of paternal age, is noteworthy because parents' age at birth is strongly bounded on the left tail of the distribution. Thus, advanced paternal age has increased considerably, extending the length of the right tail of the distribution.

The Logic of De Novo Mutations in the Context of Concordance

Putting three facts together—that *de novo* mutations are associated with neurodevelopmental disorders, parental age is associated with *de novo* mutations, and autism is associated with increasing parental age—leads one to wonder whether parental age is associated with autism via *de novo* mutations.⁸ This is the hypothesis that we directly test by focusing on the pattern of concordance across twin pairs. Other strategies for observing evidence (from population data) for a relationship between *de novo* mutations and autism focus on the sex ratio of children with autism. Following Anello et al. (2009), who showed that the sex ratio for a sample of 393 children with autism spectrum disorder (ASD) is increasingly balanced with paternal age (a sign of a potentially increased role played by *de novo* mutations), we first consider whether we observe a similar pattern in our data.⁹ Not surprisingly, we observe the same pattern. Specifically, for fathers younger than 35, the M:F ratio is 4.92 (2,841 / 13,930); for fathers older than 35, the M:F ratio is 4.38 (3,941 / 16,719). For mother's age, we observe a similar pattern (4.90 vs. 4.24). Both differences are statistically significant.

De novo mutations are extremely rare events. This fact allows us to design a critical test of the role they may play in increasing autism prevalence. Because mutations are rare events, the same *de novo* mutations should always be present in both MZ co-twins and lead to high concordance for the expression of autism. And because increasing parental age should be associated with a higher rate of *de novo* mutations, we expect rising concordance in MZ twins across time. Although counterintuitive, the rising rate of *de novo* mutations should lead to lower concordance in DZ twins over time given that such rare mutations should almost never independently co-occur in DZ co-twins, even at high parental ages.

In addition, the *de novo* mutation hypothesis has clear predictions for the changing patterns in the numbers of concordant and discordant pairs among MZ and DZ twins over time. Because *de novo* mutations are very unlikely to be shared by DZ twins, such sporadic mutations should generate discordant DZ twin pairs: concordance should decrease

8. Other factors could cause the association between parental age and autism. Older parents could choose to live in neighborhoods that are selective for autism, from environmental degradation or enhanced ascertainment; or older parents could be more worried than younger parents about their children and expose them to differential testing. Subsequently, we consider whether these competing explanations fit with the detailed evidence described in this article.

9. Interpreting the relationship between parental age and the sex ratio of children with autism as a sign of *de novo* mutations requires the assumption that *de novo* mutations affect males and females more equally than the inheritance of liability genes (Anello et al. 2009). For instance, if instead the *de novo* mutation of concern affects the inactivation of genes on the extra X chromosome—a process necessary only in girls—and if such problems with inactivation are associated with autism, then the mutation will increase the chance of autism in girls more than in boys (Brooks 2005).

as *de novo* mutations increase. Thus, we expect the OS concordance rate to decline because of an increase in the number of discordant twin pairs, while the number of concordant pairs should not be affected. It follows that examining twin concordance rates in a time of rising parental age can test the contribution of *de novo* mutations to the etiology of autism and as an explanatory factor involved in increased autism prevalence.

Increasing Heritability Over Time

Figure 1 reports SS and OS concordance rates in 1992–1994, 1995–1997, and 1998–2000. Recall that all OS twins are DZ twins, but approximately 55% of SS twins are monozygotic. Therefore, any observed trend for concordance of SS twins will be muted by the combined trends in the concordance rates in MZ and DZ twins.

As shown in Figure 1, panel A, the casewise concordance in SS twins increased over time, but it decreased in OS twins, suggesting that autism is becoming more genetically determined because of the *de novo* mutation mechanism.¹⁰ A z test of proportions was used to test for significant differences in SS and OS concordance across time. There was no significant difference in the concordance rate between SS pairs and OS pairs during 1992–1994 ($z = 1.155$, $p = .248$), but there were significant differences during 1995–1997 ($z = 2.963$; $p = .003$) and 1998–2000 ($z = 4.393$; $p = .000$). This is precisely what we expect to observe if such mutations are shaping the pattern of concordance.

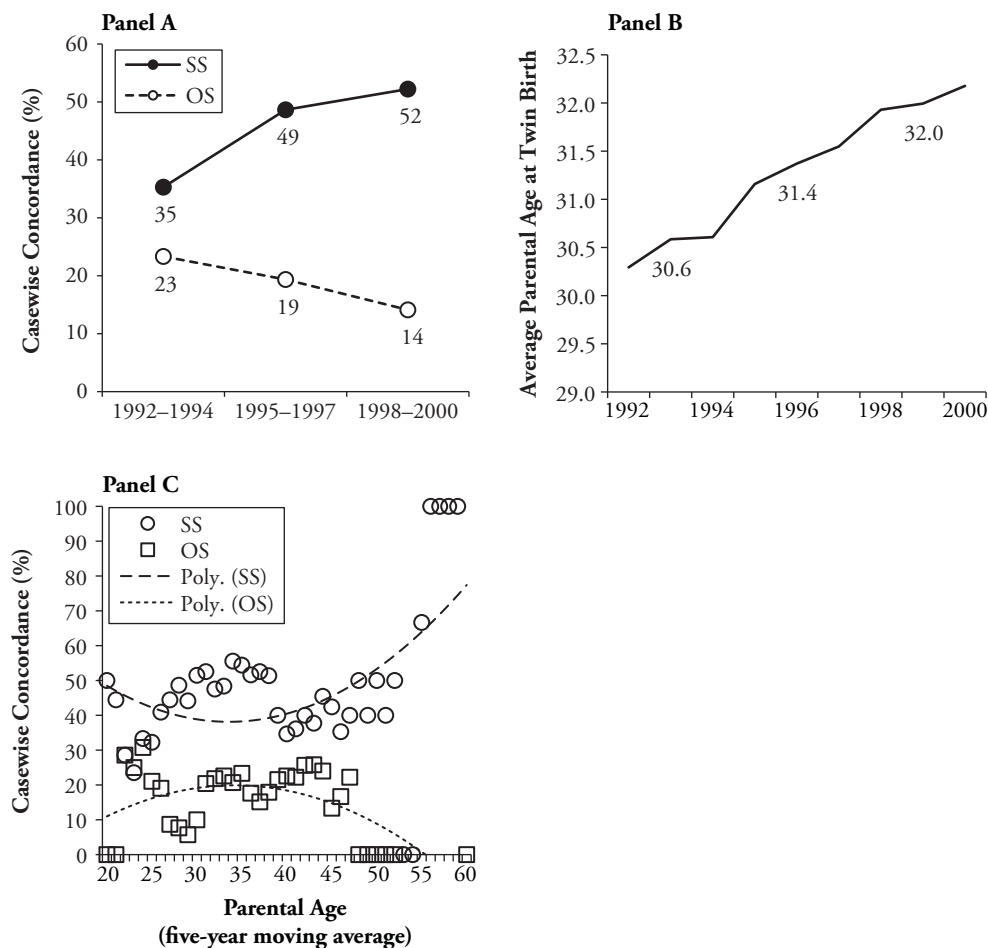
In panel B, we report change in mean parental age at twin births, which increases steadily during the same period. Recall that because MZ twins are developed from a single pair of matched egg and sperm cells, any *de novo* mutations will be found in both twins. In contrast, DZ twins develop from two distinct pairs of egg and sperm cells. Because *de novo* mutations are rare events, the chance that both DZ twins will share the same *de novo* mutation is extremely low. If *de novo* mutations have an increasing causal share in the etiology of autism over time, we should expect an increase in the difference between MZ and DZ concordance rates. One mechanism that accounts for *de novo* mutations' increasing share of autism etiology is the rise in parental age over our study period, which is likely to lead to increased mutation rates.¹¹

To test this, we fit trend lines to the five-year moving averages of the casewise concordance rates and mean parental age as shown in Figure 1, panel C. Concordance in SS twins begins to increase with parental age after 35.¹² Over the same period, OS concordance begins to decrease after age 35. The R^2 for the fitted SS line is 0.23; for the fitted OS line, 0.33. We note here that a better fit could be obtained *ex post* by fitting higher polynomials or splines. This might look better but would involve *ad hoc* theorizing. Recall that the prediction tested here is limited to older parents, and thus a square term is sufficient to capture change at the tails of the distribution. The pattern of decreasing concordance in OS twin pairs observed in Figure 1, panel C is precisely what we would expect if *de novo* mutations

10. We can estimate changing heritability by zygosity, of course. First, we need to take into account the general rise in DZ twinning rates in developed countries that have been attributed to increased use of artificial fertility treatments (Tong and Short 1998). Adjusting for the increasing proportion of DZ twins in SS pairs over time (from 42% to 47%) and assuming equal genetic liability for male and female probands, the estimated MZ casewise concordance rates increased from 37% in 1992–1994 to 75% in 1998–2000. If the genetic liability posed by female probands was 30% higher than male probands, the MZ casewise concordance rates are 41%, 59%, and 79% in 1992–1994, 1995–1997, and 1998–2000, respectively.

11. One may argue that the temporal trends in the concordance rates can be the results of other demographic trends, such as a growing population of Hispanics in California and/or rising education level. However, the diverging pattern of the concordance rates persists after Hispanics are excluded (SS casewise: 31%, 50%, and 50%; OS casewise: 28%, 22%, and 19% in 1992–1994, 1995–1997, and 1998–2000, respectively). It is also the case when we look only at the population with more than high school education (SS casewise: 41%, 49%, and 48%; OS casewise: 28%, 24%, and 13% in 1992–1994, 1995–1997, and 1997–2000, respectively).

12. The women who have children before age 35 may be different than those who have children later, given the common perception about “appropriate” maternal age in this period. But if there is this selection—which seems reasonable—we do not have a way to capture it with our data.

Figure 1. Temporal Trends of Autism Concordance and Parental Age

are associated with the increased risk of autism. Less clear is why the SS concordance should increase rapidly with parental age because the increase in SS concordance attributable to the increase in identical twins should be muted by the decrease in fraternal twins. The rapid increase in SS concordance associated with parental age may be due to a higher penetration rate among the identical twins who inherited the susceptible genotype, or other risk factors that are specific to the offspring of advanced age parents.

Finally, recall that our hypothesis also has clear predictions for the changing patterns in the numbers of concordant and discordant pairs among SS and OS twins. First, because *de novo* mutations will not be shared by OS twins, a single mutation should generate discordant twin pairs. Therefore, the OS concordance rate should decline because of an increase in the number of discordant twin pairs, while the number of concordant pairs should not be affected. This is the case. While the number of OS concordant pairs remained stable over

time, the number of discordant pairs consistently increased: there were 7, 6, and 6 concordant OS pairs and 46, 50, and 73 discordant OS pairs born in 1992–1994, 1995–1997, and 1998–2000, respectively. Turning to SS twins, we know that because a *de novo* mutation necessarily affects both twins in MZ pairs, it will follow that if the proportion of autism cases caused by such mutations increased over our study period, we should observe a surge in the number of concordant MZ pairs. However, SS twin pairs are composed of DZ and MZ twins. Consequently, if *de novo* mutations are driving increased prevalence, we would expect both rising numbers of same concordant pairs (MZ effect) and discordant pairs (DZ effect). As predicted, we observe that both concordant and discordant pairs increased during the study period: there were 15, 36, and 47 SS concordant pairs and 55, 76, and 86 SS discordant pairs in 1992–1994, 1995–1997, and 1998–2000, respectively.

DISCUSSION

This article provides substantial population-level support for the link between increasing probability of *de novo* mutations and autism. To our knowledge, no studies have examined changing concordance for autism over time.¹³ Modeling changing concordance over time allows us to construct a test of an interaction between genes and the social demographic environment that predicts increasing genetic influence. This is precisely what we observe.

Prior twin studies (Bailey et al. 1995; Folstein and Rutter 1977; Ritvo et al. 1985; Steffenburg et al. 1989) have suggested a high heritability of autism based on reports that the concordance for MZ twins is many times higher than that for DZ twins. The empirical foundations for these claims arise from absurdly small samples: adding all twin pairs from the four previous studies yields a total of only 110 pairs. All four studies relied on referrals or convenience samples, which tend to recruit similar pairs and are thus biased toward concordant twins, thus leading to inflated estimates of true concordance. In contrast, the results reported here arise from a large population-based sample. Our results show substantial MZ concordance, providing evidence that there is some genetic etiology for autism. Nevertheless, the results show that the reported high heritability for autism (> 0.9) is seriously overestimated.

A reduced heritability estimate matters because it implicates social and/or environmental drivers as playing a substantial role in the increased prevalence of autism. Prenatal factors are likely to be important environmental drivers. Concordance for OS twins and full siblings ought to be equivalent from a genetic perspective because DZ twins are full siblings who happen to be born at the same time. This is not the case. The observation that the OS concordance rate in twins is 2 to 3 times higher than the recurrence risk in full siblings suggests the importance of risk factors related to the prenatal environment or the larger social environment.

Although the genetic influence on autism has been overestimated, it has increased over time due to non-allelic mechanisms. Although the human gene pool does not change substantially over one or two generations, *de novo* germ-line mutation rates are much more susceptible to rapid social and/or environmental changes (such as rising parental age), and thus can explain the increase in the heritability of autism. Of importance is the fact that although age of parents at birth of twins was significantly higher in 2000 than in 1992, age of parents at the birth of their second-born did not increase over the same period. Thus, the difference between the trends of OS twin concordance and full-sibling recurrence risk may be associated with age of parents. Since the use of assisted reproductive technologies (ART) is associated with the age of parents and has increased radically over the same time period, ART may be implicated in the increased prevalence of autism. Our data show that the increase in the percentage of children with autism born in multiple

13. To our knowledge, no studies have considered changing concordance of anything over time. This is one reason why a sociological lens on genetics is useful.

births (from 3.6% in 1992 to 5.7% in 2000) exceeded that of the percentage of multiple births in all births in California (from 2.1% in 1992 to 2.9% in 2000). This implication requires future investigation.

It remains possible that other factors have contributed to the diverging trends in the SS and OS concordance. A virus or a toxicant experienced *in utero* could yield the results that we observe. Specifically, an increasingly prevalent virus (or toxicant) associated with a small risk of autism would lead to increasing concordance of SS twins (who often share the same placenta) and decreasing concordance of OS twins. Similarly, interactions between genes and an increasingly common environmental trigger could also generate the same pattern. However, we believe that an increase of *de novo* mutations attributable to rising parental age is more parsimonious given the documented rise in parental age, recent findings that link *de novo* mutations and autism, and the observed associations between concordance rates and parental age reported in this article.

The temporal concordance trend reported in this article is not predicted by a diagnostic expansion theory. If ascertainment and surveillance dynamics rest behind the increase in SS concordance, we would expect to observe increasing rather than decreasing concordance for OS twin pairs over time. The observation of decreasing concordance over time in OS twins challenges the idea that the results we observe are an artifact of reduction of error in diagnosis as a consequence of enhanced surveillance or clearer understanding of diagnostic markers. First, there is no evidence that diagnostic errors have been reduced; second, if this were the case, we should observe the same effect across all pair types. Finally, increasing ascertainment and surveillance would predict heightened recurrence risk for siblings over time. We do not observe any increase in such risk (chi-square statistics of linear trends in proportion = 1.613; $p = .204$).

Instead, we observe how a relatively subtle social change—namely, the population-level shift in mean age of parents at birth of their twins—is associated with enhanced risk of autism. This suggests that our image of gene-environment interactions needs to be substantially broadened to include in the relevant environment a broad array of fundamental social processes that together make up the social structures in which we live and shape the health outcomes that we—and our children—experience.

For social scientists, there are three important discoveries. First, we show that a sociological eye on the role of genetics yields the insight that *de novo* mutations may play a significant role in autism etiology. Only by observing changing patterns of concordance over time—that is, historicizing genetic influences rather than essentializing them—could we find evidence of a new causal mechanism underlying autism. Second, by working with a large population-based data set, versus small clinical samples, we have been able to properly estimate the true heritability of autism. These estimates show that autism is far less heritable than previously thought and consequently, explanations for the precipitous increase in prevalence must turn toward environmental and social dynamics often ignored by the scientific research community. Third, we show that the identification of the mechanisms by which social processes operating at the macro level—in this case, increases in parental age—“get under the skin” and shape health outcomes is a proper social science activity.

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